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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

JOHNSON, N  
ART UNIT PAPER NUMBER

1806

8

DATE MAILED: 03/25/97

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

### OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/20/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

- ☒ Claim(s) 1-50 is/are pending in the application.  
Of the above, claim(s) 1-5, 16-50 is/are withdrawn from consideration.  
☐ Claim(s) \_\_\_\_\_ is/are allowed.  
☒ Claim(s) 6-15 is/are rejected.  
☐ Claim(s) \_\_\_\_\_ is/are objected to.  
☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.  
☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.  
☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.  
☐ The specification is objected to by the Examiner.  
☐ The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).  
☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.  
☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_  
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- ☒ Notice of Reference Cited, PTO-892  
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 5  
☐ Interview Summary, PTO-413  
☒ Notice of Draftsperson's Patent Drawing Review, PTO-948 - supplemental  
☐ Notice of Informal Patent Application, PTO-152

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1. Applicant's election with traverse of Group III, Species A in Paper No. 7, filed 12/17/96 is acknowledged. The traversal is on the ground(s) that Groups I-IV are related and that examination of all groups would not pose an undue burden. This is not found persuasive. The applicant has pointed to no errors in the restriction requirement set forth in Paper No.6. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is adhered to.

The requirement is still deemed proper and is therefore made FINAL.

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

3. Updating of the status of all cited U.S. applications is requested, for example on pages 8, 12 and 32.

4. Claims 8-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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a. Claims 8 and 9 are vague and indefinite in the recitation "fragments thereof." The nature of the claimed fragments is unclear. Does the claim encompass, for example, random peptide fragments, single amino acid fragments, Fc fragments or antigen binding fragments of the claimed antibodies? Thus, the metes and bounds of the claim are unclear.

b. Claims 9 and 12 are vague and indefinite in the recitation "chimeric." The metes and bounds of the claim are unclear. Is the claimed antibody a chimeric of a variable region from one species and a constant region from another species? Or is it a chimeric molecule of an entire antibody fused to another molecule, such as a detectable marker?

c. Claims 11 and 14 are vague and indefinite in the recitation "binds to the epitope of." Does the claimed antibody bind to the same antigenic epitope that the A2 or cA2 antibodies bind? Or, does the claimed antibody bind to an epitope formed by the A2 or cA2 antibody itself, for example, the constant region or the variable region (an idiotypic determinant)?

d. Claim 11 is vague and indefinite in the recitation "A2." This is a laboratory recitation and not an art accepted term. Other products could also be called A2. The applicant is advised to amend the claim to recite the ATCC accession number.

e. Claims 14 and 15 are vague and indefinite in the recitation "cA2," which is a laboratory designation. Please see section d, above.

f. Claims 10 and 13 are vague and indefinite in the recitation "binds to one or more amino acid residues of TNF $\alpha$  selected from the group consisting of about 87-108 and about 59-

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80.” This is an improper Markush group. It is unclear how the amino acid residue is selected from groups consisting of two different peptides.

g. Claims 6 and 7 are vague and indefinite in the recitation “thrombotic disorder.” The metes and bounds of disorders encompassed by “thrombotic”, is unclear.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell lines that produce the A2 and cA2 antibodies. It is not clear that antibodies possessing the identical properties of A2 and cA2 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal

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antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibodies, a suitable deposit for patent purposes, evidence of public availability of the claimed antibodies or evidence of the reproducibility without undue experimentation of the claimed antibodies, is required.

Applicant's referral to the deposit of the cell line producing cA2 on page 16 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

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This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

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If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

6. Claims 11 and 14-15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

7. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure commensurate with the scope of the claims.

a. Claims 6 and 7 are broadly drawn to a method of treatment comprising the administration of a tumor necrosis factor "antagonist." The specification exemplifies only methods that comprise the administration of one specific tumor necrosis antagonist, antibodies specific for tumor necrosis factor. The specification states that "as used herein, a tumor necrosis antagonist decreases, blocks, inhibits, abrogates or interferes with TNF activity *in vivo*" (see p. 7, lines 6-9). "A suitable TNF antagonist can also prevent or inhibit TNF synthesis and/or TNF

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release" (see p. 78, lines 11-13), and "A suitable TNF antagonist can also prevent or inhibit TNF receptor signaling" (p. 7, lines 23-25). These definitions encompasses a very broad range of compounds, with varying methods of administration. It would require undue experimentation of one of skill in the art to identify TNF antagonists effective in the claimed method and it would be unpredictable that they would be effective in the claimed treatment method, when administered by the means disclosed in the specification. Thus, one of skill in the art could not practice the claimed invention commensurate with the scope of the claims, with a reasonable expectation of success.

b. Claim 6 is drawn to a "method for treating or preventing a thrombotic disorder" and claims 7-15 are broadly drawn to a treatment methods wherein the thrombotic disorder is selected from the group consisting of : a thromboembolic disorder, a ischemic event, a stroke, acute myocardial infarction, deep vein thrombosis and thrombophlebitis.

The specification demonstrates that the administration of anti-tumor necrosis  $\alpha$  antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels to a range closer to "normal," "that the inhibition of the biological activity of tumor necrosis factor  $\alpha$  reduces fibrinogen and platelets levels in individuals with active rheumatoid arthritis" (see p. 2, lines 14-18). This showing is used to support claims broadly drawn to the treatment of "thrombotic disorders." No *in vitro* or *in vivo* evidence is provided that the administration of tumor necrosis antibodies are effective in the treatment of any examples of a thrombotic disorder.



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The applicant provides evidence documenting the higher than normal death rate in rheumatoid arthritis patients from cardiovascular and cerebrovascular disease (abstract, Wolfe et al, Arthritis and Rheumatism 37:481-494, 1994, PTO 1449 #AT) and includes a publication stating the "fibrinogen contributes to both pathological and clinical manifestations of ischemic heart disease," and citing a studies showing a correlation "between the fibrinogen level and the extent of coronary artery disease" (see abstract, Meade, European Heart Journal 16:32-35, 1995, PTO 1449 #AU). However, this information does not provide a reasonable expectation of success for the claimed method, that the administration of anti-tumor necrosis antibodies will be effective in the treatment of thrombotic disorders in a wide patient population. This is supported by statements by Meade, that "establishing the value of agents that lower fibrinogen is now a high research priority, mainly for clinical reasons but also as part of the evidence for clarifying the nature of the association of raised levels with arterial disease (see abstract). Thus, it is not art accepted that the administration of an agent that reduces fibrinogen levels will be an effective clinical method for the treatment of thrombotic disorders and one of skill in the art could not practice the claimed invention with a reasonable expectation of success.

c. Claim 6 is drawn to a "method for treating or preventing thrombotic disorder." The specification exemplifies a treatment method that involves the administration of anti-tumor necrosis antibodies to rheumatoid arthritis patients. The specification provides no definition of "thrombotic disorder." Lacking such guidance, one of skill in the art can not identify

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“thrombotic disorders” and can not practice the invention commensurate with the scope of the claims.

d. Claims 8 and 9 are drawn to “fragments thereof” of an anti-tumor necrosis antibody. The specification provides guidance for the preparation and identification of “fragments thereof” for use in the claimed method of treatment. An almost limitless variety of “fragments” can be prepared from anti-tumor necrosis antibodies, by a wide range of methods; for example, antigen-binding fragments, Fc fragments, random peptide fragments and single amino acid fragments. In the additional guidance, it would require undue experimentation for one of skill in the art to practice the invention commensurate with the scope of the claims.

e. Claims 10 and 13 are drawn to antibodies that bind “to one or more amino acid residues of TNF $\alpha$  selected from the group consisting of about 87-108 and about 59-80.” This claim can be broadly interpreted to antibodies that bind to a single amino acid residue selected from the region of the TNF protein determined by amino acids 87-108 or 59-80. The specification provides no guidance for the preparation of such an antibody. It is well known in the art that antibodies bind to a region comprised of several amino acid residues, not to regions comprised of single amino acid residues. With out additional guidance, one of skill in the art could not practice the invention commensurate with the scope of the claims without undue experimentation.

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8. Claims 6-15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 6 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 5,547,979 published August 20, 1996 and filed April 19, 1995. U.S. Patent 5,547,979 discloses a method of treating myocardial infarction with antagonists of tumor necrosis factor that is the same as that claimed (see claim 1). For examination purposes, "antagonist" and "inhibiting agent" are taken to be art accepted equivalent terms, as both are drugs that counteract the action of another drug.

11. Claims 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,436,154, published July 25, 1995 and filed December 13, 1991. U.S. Patent Number 5,436,154 discloses a method of treating an ischemic event (myocardial ischaemia) that is the

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same as that claimed (see column 7, lines 6-17). Column 4, lines 28-42 discloses the use of chimeric antibodies in the treatment method (claim 8).

12. Claims 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Squadrito et al. (Eur. J. Pharmacology 237:223-230, 1993). Squadrito discloses a method of treating an ischemic event (myocardial ischaemia-reperfusion injury) with the administration of antibodies to tumor necrosis factor (see abstract) that is the same as that claimed.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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14. Claims 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of U.S. Patent Number 5,436,154, published July 25, 1995 and filed December 13, 1991 or Squadrito et al. (Eur. J. Pharmacology 237:223-230, 1993) in view of WO 92/16553 (published October 1, 1992).

The teachings of Patent Number 5,436,154 and Squadrito et al., for a method of treating ischemic events or myocardial infarction with antibodies to tumor necrosis factor have been previously discussed in paragraphs 11 and 12, above. Patent Number 5,436,154 and Squadrito et al. do not teach the use of the A2 antibody or the cA2 chimeric antibody in the method of treatment.

However, WO 92/16553 teaches both the A2 and cA2 antibodies (see p. 9, line 29 and p. 61, line 21), antibodies which recognize an epitope containing TNF amino acid residues 87-108 or 59-80 (see p. 7, lines 29-32).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the A2 and cA2 antibodies, as taught in WO 92/16553 in the treatment methods taught in either of Patent Number 5,436,154 and Squadrito et al., which utilize antisera to tumor necrosis factor.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of WO 92/16553; on the high binding affinity of the A2 antibody (see p. 9, line 29) and the usefulness of chimeric antibodies, such as cA2, in

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overcoming the "problems of murine antibody immunogenicity" and to "provide reduced immunogenicity and increased neutralization activity" (see p. 7, lines 14-17).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy A. Johnson, Ph.D. whose telephone number is (703) 305-5860. The examiner can normally be reached on Monday-Friday from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax number for the group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Nancy A. Johnson, Ph.D.

March 17, 1997



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